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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/840,872 | 04/25/2001 | Antonio J. Grillo-Lopez | P 0280609/2000-30-154A | 4921 |

909 7590 07/26/2004

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| EXAMINER | |
|---|---|
| NICKOL, GARY B | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/840,872 | GRILLO-LOPEZ, ANTONIO J. | |
| | Examiner | Art Unit | |
| | Gary B. Nickol Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Grillo-Lobez, A.

Date of priority: 04/25/2000

***Response to Amendment***

The Amendment filed 05/12/04 in response to the Office Action of 12/12/03 is acknowledged and has been entered.

Claims 61-67 were added.

Claims 56-67 are currently under consideration.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

**Rejections Maintained:**

Claims 56-60 remain rejected and new claims 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,776,456 (Anderson *et al.*) in view of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252).

(The limitation of new claims 63-67 are anticipated by Anderson *et al.* via the teaching of the anti-CD20 antibody "C2B8", also referred to as rituximab in the specification on page 20)

Applicant's appear to primarily argue how the different routes (i.e. systemic, intrathecal, intraventricular) of administering the anti-CD20 antibody would not lead one of ordinary skill in the art to reasonably predict that "elevated levels of anti-CD20 antibody in cerebrospinal fluid could be achieved". For example, applicants argue that routine techniques for administration of antibodies simply do not result in levels of antibody that are higher in cerebrospinal fluid than in serum wherein the Pels *et al.* reference teaches that antibody concentrations in cerebrospinal fluid are low after routine systemic administration (abstract). Applicants further introduce the teachings of Harjunpää *et al.* which state that an intact blood-brain barrier restricts antibody entry in to the CNS. These arguments have been carefully considered but are not found persuasive because the broad scope of the claims are not limited to any particular route of administration. In fact, the combined teachings of applicants' references only appear to teach away from administering antibodies either systemically or intravenously for the purposes of targeting cancerous cells located in the central nervous system. This, however, does not disenable or otherwise render nonobvious the administration of the antibodies *directly* to the site of the tumor, i.e. intralesionally, intrathecally or intraventricularly. In fact, the teachings of Caligiuri *et al.* suggest these routes of administration for treating central nervous system lymphomas (column 15, line 12).

In contrast with the above, however, applicants further submit that intrathecal administration techniques do not predictably result in cerebrospinal fluid levels that are higher than serum levels. However, the submitted teachings of Cokgor *et al.* and Blaney *et al.* do not offer sufficient evidence to validate applicant's arguments. For example, the fact that intraventricular administration may be associated with infection, catheter occlusions and

meningitis does not provide a substantial nexus to any observable differences in antibody levels between CSF and serum following intraventricular administration. Furthermore, the passages referred to in Cokgor *et al.* and Blaney *et al.* do not parallel the pending claims because they concern the administration of chemotherapeutics that are structurally and functionally distinct from an anti-CD20 antibody.

Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

Claims 56-60 remain rejected and new Claims 61-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,776,456 (Anderson *et al.* ) in view of the teachings of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252) for the reason of record. Applicants reiterate their arguments as set forth above. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

**All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.**

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN
July 21, 2004

GARY NICKOL
PRIMARY EXAMINER